from these 13 cohort studies. The 13 studies pooled by Kapoor et al[2] included both 10 cohorts of "noncardiac surgery" and three cohorts of "cardiac surgery." The pooled OR from the 10 studies of "noncardiac surgery" was 0.70 (95% CI, 0.53 to 0.91). Furthermore, these 10 cohorts of "noncardiac surgery" included six studies of "major (noncarotid) vascular, noncardiac surgery" (eg, repair of abdominal aortic aneurysm, aorto-femoral bypass, and infrainguinal revascularization), two studies of "carotid endarterectomy," one study of both "carotid endarterectomy" and "major (noncarotid) vascular, noncardiac surgery," and one study of "thoracic surgery."

We combined the data from the above-mentioned homogenous six cohort studies[3-8] of "major (noncarotid) vascular, noncardiac surgery" (380 events in 4865 patients) using a random-effects model, which gave a summary OR of 0.74 (95% CI, 0.54 to 1.01; $P = .0590$) with statin use. There was neither trial heterogeneity of results analyzed by means of standard $\chi 2$ tests ($P = .2602$) nor evidence of significant publication bias assessed using an adjusted rank-correlation test ($P = .8510$). Therefore, routine administration of statins does not reduce perioperative cardiovascular risk in "major (noncarotid) vascular, noncardiac surgery."

Hisato Takagi, MD, PhD
Toshiyuki Tanabashi, MD
Norikazu Kawai, MD
Takuya Umemoto, MD, PhD

Department of Cardiovascular Surgery
Shizuoka Medical Center
Shizuoka, Japan

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Reply

We appreciate the interest of Dr Takagi and colleagues regarding our publication "Statins for the prevention of perioperative cardiovascular complications in vascular surgery".

First, we would like to point out that the only double blind randomized trial published so far that specifically investigated the effect of statins on perioperative cardiovascular outcome showed a significant beneficial effect of perioperative statin use (8% vs 26% cardiovascular complications, $P = .03$).[1]

Second, why did Dr Takagi and colleagues only use six retrospective studies for their analysis? We agree that including studies reporting on carotid surgery only[2] in their systematic review would be incorrect. However, the study by O'Neil-Callahan et al[3] should have been included in their review since this study included 177 aortic and 622 lower extremity arterial surgical procedures. If these 799 patients would have been added to the analysis of Takagi and colleagues, the odds ratio would be 0.71 with 95% confidence intervals of 0.57 to 0.88 and P for homogeneity of .313. This suggests a beta-II error of the presented analysis by Dr Takagi. If all appropriate studies were taken into account, statins would have provided a highly significant beneficial effect on postoperative outcome in patients undergoing major vascular surgery.

Third, current American College of Cardiology/American Heart Association (ACC/AHA) treatment guidelines recommend statin use for patients at increased cardiovascular risk.[4] In fact these guidelines have as a class 1 recommendation "treatment with a hydroxymethyl glutaryl coenzyme-A reductase inhibitor medication is indicated for all patients with peripheral arterial disease to achieve a target low-density lipoprotein (LDL) cholesterol level of less than 100 mg per dl." As all patients scheduled for major vascular surgery have peripheral arterial disease, it would be prudent to install treatment at the first vascular surgery outpatient clinic visit. In particular, since current evidence does suggest that there is no increased risk for myopathy or rhabdomyolysis in patients on statin therapy undergoing major vascular surgery.[5]

In conclusion, if a proper meta-analysis of all cohort studies reporting on cardiac outcome in statin or nonstatin users undergoing major vascular surgery is performed, the results show a highly significant beneficial effect of statins. This result is supported by the only double blind randomized trial published on this subject to date. Consequently, we still believe that routine administration of statins in patients undergoing major vascular surgery reduces perioperative cardiovascular risk.

Olaf Schouten, MD
Sanne E. Hoeks, MSc
Anai E. S. Durazzo, MD
Don Poldermans, MD, PhD

Department of Vascular Surgery, Cardiology, and Anesthesiology
Erasmus MC
Rotterdam, The Netherlands

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ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006;47:1239-312.

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Regarding "Elevated C-reactive protein levels are associated with postoperative events in patients undergoing lower extremity vein bypass surgery"

Owens et al[1] have reported the results of a prospective study on the prognostic significance of C-reactive protein (CRP) in patients undergoing lower extremity vein bypass surgery. They stated that this is the first study demonstrating the role of this inflammatory marker on the outcome of patients with lower limb ischemia.

Indeed, about 15 years ago, Majewski et al were the first to suggest the prognostic value of CRP in patients with chronic[2] as well as acute lower limb ischemia.[3] The latter findings were nicely confirmed by Kuukasjärvi et al.[4] More important, Upchurch et al[5] were the first to demonstrate a clear correlation between CRP and the severity of foot ulcers.

This prompted us to investigate this issue in patients undergoing infrainguinal bypass surgery.[6-8] These studies showed that CRP not only was clearly correlated with the severity of lower limb ischemia but also with infection due to some bacterial strains.[6] CRP came out as one of the most important determinants of several postoperative outcome end points.

However, these findings, as well as the extremely elevated levels of CRP in patients with critical limb ischemia, suggest that CRP cannot be considered as a marker aggressive atherosclerosis, but rather as a marker of the severity of lower limb atherosclerosis and its related ischemic complications. This also suggests that in these patients, CRP is not likely to be a major determinant of vein graft disease but rather that increased CRP is associated with severe critical limb ischemia and with other extrinsic determinants of graft failure. Interestingly, preoperative levels of CRP were markedly increased, especially in those patients who required lower limb amputation despite a patent graft.[7,8]

Fausto Biancari, MD, PhD

Division of Cardio-thoracic and Vascular Surgery
Department of Surgery
Oulu University Hospital
Oulu, Finland

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Reply

We appreciate the interest and concerns of the correspondents regarding our article "Elevated C-Reactive Protein Levels Are Associated With Postoperative Events in Patients Undergoing Lower Extremity Vein Bypass Surgery." As they point out, a number of authors have previously demonstrated an association between C-reactive protein (CRP) levels and the severity of peripheral arterial disease, including complications related to critical limb ischemia; our results are but another confirmation in this regard. These studies vary in the heterogeneity of the study populations and, importantly, in the use of the current high-sensitivity assay (hsCRP) used in these studies. However, the unique focus of our investigation was to examine the relevance of inflammatory biomarkers such as hsCRP to the outcomes of vein bypass surgery in the limb.

As stated in the introduction, our hypothesis is that chronic, low-grade, systemic inflammation is directly related to the development and progression of vein graft disease.[1] CRP is increased in acute infection, cancer, and systemic illness, and it is associated with diabetes, renal failure, and critical limb ischemia. We did not intend to measure the effects of acute increases in CRP attendant with severe infections or extensive necrosis. Accordingly, our study design specifically excluded patients who had evidence of clinical infection, immunocompromised states, or systemic illness such as recent myocardial infarction.[1] The median hsCRP concentration in our study population was 3.25 mg/L. By contrast, the other cited studies[2-4] included reconstruction procedures with mixed conduits, including prosthetic, and were not designed to evaluate associations with failure of autogenous conduits.[2-4] More importantly, the study populations seem significantly different from ours in terms of the inclusion of patients with severe, acute inflammation. For example, in the referenced studies, the median CRP in patients having an amputation was greater than 40 mg/L and was greater than 100 mg/L in those having an amputation despite an open graft; these values are an order of magnitude larger than those observed in our cohort.[2-4] These authors concluded that patients undergoing pedal bypass who have a CRP greater than 100 mg/L have a twofold risk for limb loss at 1 year.[2] Although lacking an explicitly stated hypothesis,[2,3] it seems likely these studies evaluate CRP as a biochemical surrogate for the degree of lower extremity tissue loss and/or infection, which might then influence limb salvage by failures not specific to revascularization.

In our published article, we reported that among a cohort of 91 patients undergoing autogenous vein reconstruction, a baseline level of hsCRP greater than 5 mg/L (the upper reference level in our laboratory) was predictive of subsequent major cardiovascular events, the majority of which were vein graft related.[1] This relationship was maintained on multivariate analysis when confounding factors were controlled. In an updated analysis that included more patients (n = 147) and additional observation time, patients with elevated baseline hsCRP (>5 mg/L) experienced more vein